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THE EFFECTS OF LONG-ACTING METHYLPHENIDATE FORMULATIONS AND ATOMOXETINE ON CARDIAC FUNCTIONS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY

DİKKAT EKSİKLİĞİ VE HİPERAKTİVİTE BOZUKLUĞU OLAN ÇOCUKLARDA UZUN ETKİLİ METİLFENİDAT BİLEŞİKLERİNİN VE ATOMOKSETİNİN KARDİYAK FONKSİYONLAR ÜZERİNDEKİ ETKİLERİ

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ABSTRACT

Objective: Methylphenidate (MPH) and atomoxetine (ATX) are most commonly prescribed for the treatment of attention deficit hyperactivity disorder (ADHD). In the literature, there are studies performed to evaluate each of these drugs, but there is no study comparing these three medications together. Therefore, we aimed to evaluate the cardiac effects of these medications.

Methods: Forty-six children with ADHD using osmotic-release oral system MPH (OROS-MPH), 46 using extended-release MPH (ER-MPH), and 46 using ATX for at least six months were included in the patient groups. Forty-six children with normal cardiac findings were enrolled as the control group. All participants were evaluated using a sociodemographic information form, 12-channel electrocardiography (ECG), transthoracic 2D, Doppler and tissue Doppler echocardiography.

Results: Statistically significant differences were observed in terms of A wave velocity, E/A and E' septal values between the groups (p=0.002, p<0.001, p=0.002, respectively). Children using ATX had higher A wave velocities than the OROS-MPH users and controls (p<0.001 and p=0.007, respectively) and lower E/A values than the OROS-MPH users and controls (p<0.001 for both). Children using ER-MPH and ATX had lower E' septal values compared to the control group (p<0.001 and p=0.002, respectively).

Conclusion: Atomoxetine treatment showed impairment in some of the myocardial relaxation parameters more than long acting-MPH medications. In conclusion, although the drugs used in the treatment of ADHD are cardiac safe in general and do not cause clinical findings of heart failure, patients should be evaluated for cardiac involvement. Further studies are needed to support the findings in our study.

Anahtar Kelimeler: Methylphenidate, Atomoxetine, children, tissue Doppler imaging, attention deficit and hyperactivity disorder.

ÖZ

Amaç: Dikkat Eksikliği ve Hiperaktivite Bozukluğunun (DEHB) tedavisinde metilfenidat (MPH) ve atomoksetin (ATX) en yaygın olarak reçete edilen ilaçlardır. Literatürde bu ilaçların kalp üzerine etkilerini tek tek karşılaştıran çalışmalar olmakla bu üç ilacı birlikte karşılaştıran çalışmalar yoktur. Dolayısıyla bu çalışmada DEHB tedavisinde kullanılan bu ilaçların kalp üzerine etkilerini karşılaştırmayı amaçladık.

Yöntem: Hasta gruplarına en az 6 aydır ozmotik-salınımlı oral sistem metilfenidat (OROS-MPH) kullanan 46 hasta, geç-salınımlı metilfenidat (ER-MPH) kullanan 46 hasta ve ATX kullanan 46 DEHB tanılı çocuk dahil edildi. Normal kardiyak bulguları olan 46 çocuk kontrol grubu olarak alındı. Tüm katılımcılar sosyodemografik bilgi formu, 12 kanallı elektrokardiyografi (EKG), transtorasik 2D, Doppler ve doku Doppler ekokardiyografi kullanılarak değerlendirildi.

Bulgular: Gruplar arasında A dalga hızı, E/A ve E' septal parametrelerinde istatistiksel olarak anlamlı fark izlendi (p=0,002, p<0,001, p=0,002, sırasıyla). Atomoksetin kullanan çocuklarda, OROS-MPH kullananlara ve kontrollere göre daha yüksek A dalga hızı (p<0,001, p=0,007, sırasıyla) ve OROS-MPH kullananlara ve kontrollere göre daha düşük E/A (p<0,001, her ikisi için) saptandı. Geç-salınımlı metilfenidat ve ATX kullanan çocukların E' septal değerleri kontrol grubuna göre daha düşüktü (p<0,001, p=0,002, sırasıyla).

Sonuç: Atomoksetin tedavisi, bazı miyokardiyal relaksasyon parametrelerinde uzun etkili MPH tedavilerine göre daha fazla bozulmaya sebep olmuştur. Sonuç olarak, DEHB tedavisinde kullanılan ilaçlar genel olarak kardiyak açıdan güvenli olsalar ve klinik olarak kalp yetersizliğine sebep olacak sonuçlar doğurmasalar da hastalar kardiyak açıdan değerlendirilmelidirler. Çalışmamızdaki sonuçları desteklemek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Metilfenidat, Atomoksetin, çocuklar, doku doppler görüntüleme, dikkat eksikliği ve hiperaktivite bozukluğu

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Introduction

Attention deficit and hyperactivity disorder (ADHD) is a psychiatric condition presenting with hyperactivity, inattention and impulsivity.[1] It affects 5-7% of school-age children.[2] The prevalence is three times higher in boys than in girls.[1] Stimulant and non-stimulant drugs are used for treatment.[2] One of the best known stimulant medications is methylphenidate (MPH), while non-stimulant medication therapy is provided with atomoxetine (ATX). There are different forms of MPH, such as immediate-release (IR-MPH), extended-release (ER-MPH), and osmotic-release oral system methylphenidate (OROS-MPH).[3]

Treatment with psychostimulant drugs is usually the option of choice, with once-daily doses of OROS-MPH and ER-MPH producing higher adherence to therapy than IR-MPH, which is administered three times a day. Atomoxetine involves similar effects and dosages to those of long-acting forms of MPH.[4] Osmotic release-MPH (Concerta®) (Janssen-Cilag Ltd, High Wycombe, UK) uses the osmotic controlled-release delivery system³. It dissolves within 1 to 2 hours and releases 22% of the total dose of MPH. The remaining 78% of the dose is osmotically controlled (osmotic-release oral system technology) and is released over 10 hours. The maximum effect occurs 6 - 8 hours after dosing.[5] Extended release-MPH (Medikinet® retard, MEDICEPharma GmbH and Co., KG, Iserlohn, Germany) provides 50% of the racemic dose immediately, the remaining 50% being released over 12 hours.[6] The maximum effect occurs 8 hours after dosing.[7] Atomoxetine (Strattera®, The Netherlands) is one of the non-stimulant drugs and can be administered once or twice-daily.[8]

Methylphenidate exhibits its effects by blocking dopamine and noradrenaline transporters, thus increasing the concentrations of dopamine and noradrenaline in the presynaptic region.[1,2] Atomoxetine is a selective inhibitor of noradrenaline transporters that regulates noradrenaline transmission by inhibiting the reuptake of noradrenaline into presynaptic nerve terminals. This in turn causes the effects of sympathomimetic amines such as noradrenaline and dopamine to appear in the body.[8]

Increased sympathomimetic impacts are expected to be observed in different systems of the body.[3] In general, heart rate (HR), blood pressure (BP) and, electrocardiographic findings have previously been investigated. There are also case reports showing that these psychostimulant drugs affect cardiac functions and precipitate myocardial infarction.[6,9,10,11] Several reports have also suggested that increasing sympathetic activity or low parasympathetic activity exacerbate the risk of sudden cardiac death, independently of other risk factors.[12] A study evaluating the cardiac safety of these drugs showed that methylphenidate usage revealed no significant association with either cardiovascular events like angina, dysrhythmia or transient cerebral ischemia.[13] They stated that clinical diagnoses of cardiovascular events and symptoms were rare and not associated with stimulant use.[13] Another study was performed in children who use MPH to investigate cardiovascular functions by echocardiography. They revealed that there was no clinical differences between the children using MPH and controls declaring that MPH usage does not impair cardiovascular functions at short-term follow-up.[14] But there has been no pediatric studies evaluating and comparing the effects of the these three widely used medications together on diastolic and systolic cardiac functions. Therefore this study was performed to investigate the effects of MPH formulations and ATX on cardiac functions in pediatric patients with ADHD.

Methods

Study design

Forty-six children with ADHD using OROS-MPH (Concerta®), 46 using ER-MPH (Medikinet® retard), and 46 using ATX (Strattera®) were included in the study. Additionally, 46 healthy children without any disease were included as the control group. All the patients with ADHD had been using their medications for at least six months. The patient groups and control group were matched in terms of weight, age, and gender parameters. None of the patients enrolled in the study experienced any significant adverse events requiring drug discontinuation. All participants were evaluated using a sociodemographic information form prepared by experienced researchers. Patients with any known systemic disease or using drugs other than MPH or ATX were excluded from the study. Children were also excluded in case of a contraindication to any of the medications, or if another drug combination was required. Individuals capable of completing the questionnaires and with no sensorial deficit capable of obstructing communication with the psychiatrist were included in the patient group. They were interviewed about cardiovascular adverse events such as chest pain, palpitation, and syncope and non-cardiac adverse events such as nausea, abdominal pain, decreased appetite, and headache. All procedures were performed in accordance with the ethical standards of the relevant institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent forms were obtained from all patients and their parents. All the groups in the study were subsequently evaluated by a pediatric cardiologist by means of physical examination and electrocardiographic and echocardiographic findings. Echocardiographic evaluation was performed using conventional, color Doppler and tissue Doppler echocardiography.

Cardiac evaluation

Twelve-channel electrocardiographic evaluation was performed to all of the participants. Transthoracic echocardiographic studies were conducted by using an EPIQ 7 Ultrasound System (Philips, Heide, The

Netherlands) with S8 and S5 probes. Following echocardiographic evaluation, BP was measured using an age-appropriate sphygmomanometer. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated using the averages of three measurements.

Echocardiography

Measurements were performed using conventional and Doppler echocardiography. Left ventricular systolic functions were measured by using M-mode.[13] All echocardiographic measurements were taken in three repetitious cycles, and their mean values were calculated. M-mode records were taken at a rate of 50 mm/s, and Doppler records at 100 mm/s. Mitral early diastolic flow velocity (E), E wave deceleration time (EDT), late diastolic flow velocity (A) and its duration (A duration), and E/A were measured with the sample volume of pulse wave (PW) placed on the level of the mitral annulus in apical four-chamber view.[15,16]

Tissue Doppler imaging

All participants underwent tissue Doppler imaging examinations. Acquisition by pulsed tissue Doppler imaging was recorded at a high frame rate (>180 fr/sec) in apical four-chamber imaging at the mitral annulus. An appropriate velocity scale was chosen in order to avoid data aliasing. A sample volume of PW was placed on the conjunction of both the septal and lateral walls of the left ventricle and the mitral annulus. Peak early diastolic wave velocity septal and lateral (E'septal and E'lateral), peak late diastolic wave velocity septal and lateral (A'septal and A'lateral), E/E' septal and lateral, isovolumetric relaxation time (IVRT) septal and lateral, isovolumetric contraction time (IVCT) septal and lateral, mitral annular peak velocity septal and lateral (S' septal and S' lateral) were measured by using tissue Doppler imaging to elicit information concerning left ventricular systolic and diastolic functions.[17]

Statistical Analysis

Analyses were performed with MedCalc Statistical Software version 12.7.7 (MedCalc Software Bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Descriptive statistics were used to express continuous variables (mean ± standard deviation). Student's t test was applied in the comparison of two independent variables with normal distribution, while two independent variables without normal distribution were compared using the Mann Whitney U test. One-Way ANOVA was employed in the comparison of more than two independent variables exhibiting normal distribution. The Kruskal Wallis test was applied in the comparison of more than two independent variables without normal distribution. The chi-square test (or sometimes Fisher's Exact test) was used for evaluating relationships between categorical variables. Statistical significance (p) was determined as <0.05.

Results

The study was conducted with 184 participants, consisting of 138 cases (three groups) and 46 controls. Age, gender, weight, and height were similar between the groups, although SBP, HR, duration and dose of medication differed between the groups (p=0.001, p=0.014, p <0.001, and p<0.001, respectively). Systolic blood pressure was not higher in the patient groups than the controls, and DBP was similar in all four groups. Heart rate was higher in the ATX group than in the other groups (p=0.002). Rates of adverse events were higher in the OROS-MPH group (26.1%) than in the other groups (15.2%, 4.3%, p<0.001). Cardiac adverse events and family histories of cardiac events were similar in the groups (p>0.05). Patients using OROS-MPH exhibited a longer duration of medication than those using ER-MPH and ATX (31.9±16 months, 19.89±11.4 months, 16.2±14.43 months, respectively, p<0.001 for both). The lowest medication dosage was observed in the patients using ER-MPH (p<0.001) (Table 1 and Table 3).

A, E/A, and E' septal differed significantly between the groups (p=0.002, p<0.001, and p=0.002, respectively). The ATX group exhibited a higher A wave velocity and lower E/A than the OROS-MPH (60.65±13.22 cm/s vs 51.50±9.70 cm/s, 1.67±0.44 vs 2.02±0.4, p<0.001, for both) and control groups (60.65±13.22 cm/s vs 54.90±12.60 cm/s, 1.67±0.44 vs 1.94±0.43, p=0.007 and p<0.001, respectively). Additionally, the ER-MPH group exhibited lower E/A than the OROS-MPH group (1.75±0.52 vs 2.02±0.41 p =0.001). E' septal values were lower in both the ER-MPH and ATX groups than in the controls (13.77±2.69 cm/s vs 15.54±2.31 cm/s p<0.001 and 14.08±2.83 cm/s vs 15.54±2.31 cm/s p=0.002) (Table 2 and Table 3).

Discussion

Methylphenidate and ATX are used as first-line therapies in the treatment of ADHD. Studies investigating the cardiac safety of these drugs have reported inconsistent results. A study including 1,200,438 participants aged 2-24 years showed no evidence that medications used for ADHD lead to severe cardiovascular events such as sudden death, myocardial infarction, and stroke.[18] One potential mechanism proposed to account for severe cardiac events caused by ADHD medication involves acute tachycardia-induced cardiomyopathy. This result is usually associated with supraventricular or ventricular tachycardia, and after controlling the rhythm, cardiac functions return to normal.[13,19-21] According to the literature it is known that activation of sympathetic system triggers sudden death but there is also a different theory, which suggests that increased HR variability as a result of increased parasympathetic activity diagnosed by 24 hour Holter monitoring may be beneficial in terms of predicting the

risk of sudden cardiac death.[12] Clinical findings such as palpitation, chest pain and syncope becomes prevalent as a result of increased sympathetic activity.[12] There are studies in the literature showing that ATX and MPH had no difference in terms of adverse cardiac events.[22,23] Our patients were followed-up and asked about cardiac adverse events. Consistent with the previous literature, no difference was observed between the groups and controls in terms of cardiac adverse events in the present study. The OROS-MPH group exhibited higher rates of non-cardiac adverse events such as nausea, abdominal pain, decreased appetite, and headache than the other groups. This finding may be attributed to the longer duration of OROS-MPH use than the other medications.

Table 1. Demographic, hemodynamic and electrocardiographic characteristics of the patients

		OROS-MPH n=46 Mean ±SD Med (min-max)	**ER-MPH** n=46 Mean ±SD Med (min-max)	**ATOMOXETINE** n=46 Mean ±SD Med (min-max)	**Controls** n=46 Mean ±SD Med (min-max)	**p**
Age (year)		10.20±2.11 10 (7-16)	10.02±2.07 9 (7-16)	10.09±2.42 9.5 (6-16)	10.00±2.00 9 (7-17)	0.953
Gender (M/F)		34/12	35/11	33/13	34/12	0.995
Weight (kg)		38.00±7.00 38 (25-54)	37.22±10.89 35 (24-73)	37.13±12.54 33.5 (20-67)	37.90±10.80 34.5 (24-66)	0.180
Height (cm)		143.00±12.00 142 (104-168)	141.62±13.14 137.5 (126-176)	141.39±15.89 136 (123-183)	142.00±13.00 139 (124-175)	0.350
SBP (mmHg)		103.30±10.15 100 (90-124)	99.37±11.14 100 (75-130)	98.93±10.98 100 (80-120)	107.05±11.17 110 (85-128)	**0.001**
DBP (mmHg)		64.40±7.00 60 (49-80)	65.09±7.45 65 (50-85)	65.63±6.92 65 (50-80)	63.00±10.36 64 (41-82)	0.483
HR (min)		85.16±14.10 84 (47-113)	88.22±16.84 86 (52-129)	93.02±16.12 90 (61-132)	83.25±14.18 82 (43-113)	**0.014**
QTc (s)		0.40±0.02 0.39 (0.35-0.44)	0.39±0.07 0.39 (0.36-0.43)	0.40±0.04 0.39 (0.35-0.44)	0.39±0.03 0.4 (0.33-0.44)	0.954
Duration of medication (month)		31.9±16 30 (6-60)	19.89±11.4 19 (6-48)	16.2±14.43 12 (6-72)	-	**<0.001**
Dose of medication (mg/kg)		0.94±0.17 0.91 (0.56-1.42)	0.69±0.22 0.67 (0.27-1.25)	1.03±0.17 1 (0.67-1.4)	-	**<0.001**
Adverse event	No Yes	34 (73.9%) 12 (26.1%)	39 (84.8%) 7 (15.2%)	44 (95.7%) 2 (4.3%)	46 (100.0%) 0 (0.0%)	**<0.001**
Cardiac adverse event	No Yes	40 (87.0%) 6 (13.0%)	42 (91.3%) 4 (8.7%)	43 (93.5%) 3 (6.5%)	45 (97.8%) 1 (2.2%)	0.282
Cardiac event in family history	No Yes	32 (69.6%) 14 (30.4%)	35 (76.1%) 11 (23.9%)	31 (67.4%) 15 (32.6%)	30 (65.2%) 16 (34.8%)	0.700

Kruskal Wallis test, Fisher'sExact p<0.05 DBP: Diastolic blood pressure, F: female, HR: Heart rate, M: male, n: number, SBP: Systolic blood pressure, SD: Standard deviation, QTc: corrected QT interval, ATX: Atomoxetıne MPH: Methylphenidate, ER: extended-release, OROS: osmotic-release oral system, Bold values denote statistical significance at the p < 0.05 level

Dopaminergic effects associated with MPH are thought to increase HR and BP, with an expected rise in epinephrine levels.[24,25] It is described in the studies that the overall cardiac risks associated with ADHD medication is unimportant. According to the literature usage of MPH and ATX was associated with small elevations of BP and HR with no changes in electrocardiographic parameters[26,27] In contrast, increase in HR and SBP more than controls was stated with stimulant therapy and in the ATX group more than the MPH group.[1] An open study consisting of children aged 6-17 years, reported that OROS-MPH caused no significant increase in SBP, while ATX was associated with significant increases in DBP and HR.[28] In the present study, HR was higher in the ATX group than the controls, with no differences between the long–acting MPH drugs and accompanied with similar BPs.

Dopamine is thought to alter left ventricular filling pressures by raising the pressures supported by alpha receptor-mediated arterial vasoconstruction.[29] In addition to the expected increase in HR and BP described in some studies, these variables can also alter cardiovascular hemodynamics. Accordingly, we examined cardiovascular involvement in this study. Thickening of the posterior wall or interventricular septum is important in terms of predicting left ventricular hypertrophy or diastolic dysfunction, and we detected no increase in ventricular wall diameters. Dilated cardiomyopathy with an ejection fraction of 25% was described in an obese 18-year old male patient associated with the use of MPH. These findings support the idea of an increased risk of heart failure after exposure to MPH.[9]

Table 2. Conventional, Doppler, tissue Doppler echocardiographic measurements of the patients

	OROS-MPH n=46 Mean ±SD Med (min-max)	**ER-MPH** n=46 Mean ±SD Med (min-max)	**ATOMOXETINE** n=46 Mean ±SD Med (min-max)	**Controls** n=46 Mean ±SD Med (min-max)	**P**
IVSd (cm)	0.74±0.12 0.7(0.5-1)	0.70±0.10 0.68(0.5-0.9)	0.71±0.11 0.7(0.5-0.9)	0.75±0.13 0.7(0.5-1)	0.135
LVEDd (cm)	3.93±0.42 3.9(3-5)	3.92±0.32 3.9(3.3-4.6)	3.85±0.52 3.8(2.95-5.4)	4.05±0.49 3.95(3.2-5.2)	0.155
LPWDd (cm)	0.71±0.13 0.7(0.5-1.1)	0.69±0.10 0.65(0.45-0.9)	0.68±0.10 0.69(0.5-1)	0.73±0.13 0.7(0.5-1)	0.190
LA (cm)	2.36±0.29 2.3(1.9-3.2)	2.30±0.30 2.3(1.8-3.1)	2.32±0.38 2.3(1.6-3.8)	2.33±0.29 2.3(1.8-3)	0.717
EF (%)	71.10±4.22 70(65-79)	72.39±4.35 73(65-81)	71.09±4.04 71.5(65-78)	73.15±4.26 73(65-82)	0.078
FS (%)	40.34±4.70 39(35-49)	41.02±3.59 41(35-49)	40.09±3.20 40(35-46)	42.11±4.67 41(35-51)	0.128
E (cm/s)	101.30±14.8 102(59.4-134)	99.77±16.06 99(72-138)	96.93±13.4 94.85(74.2-135)	103.00±16.90 100(66-144)	0.273*
A (cm/s)	51.50±9.70 52.2(34-70.8)	60.93±18.57 57.7(31.5-114)	60.65±13.22 60.6(28-90.7)	54.90±12.60 54(33-100)	**0.002**
E/A	2.02±0.41 2 (1.29-3.02)	1.75± 0.52 1.66(0.76-3.24)	1.67± 0.44 1.51(1.01-2.98)	1.94±0.43 1.92(1.14-2.89)	**<0.001**
EDT (ms)	109.47±15.25 107.6(86-158.96)	103.65±17.81 99.41(70-155)	103.07±18.96 102(44.4-146)	104.45±18.74 99.41(68.39-151)	0.264
A duration (ms)	111.38±16.28 109.65(85.03-172)	105.06±14.35 104(81-143)	104.61±16.92 104.5(63-145)	109.93±18.15 107.1(81.33-184)	0.206
S' septal (cm/s)	7.92±1.16 7.87(5.97-11)	8.51±1.25 8.36(6.58-12.3)	8.06±1.56 7.74(5.27-13.4)	8.25±1.26 8(6.96-12)	0.116
E' septal (cm/s)	14.44±2.57 14.85(9.25-20)	13.77±2.69 13.65(6.11-22.2)	14.08±2.83 14(8.22-26.4)	15.54±2.31 15(10-20)	**0.002**
A' septal (cm/s)	6.64±1.19 6.13(4-9)	7.24±1.53 7(4.25-10.8)	7.33±1.57 7.26(4.48-10.8)	7.12±1.58 7(5-15)	0.090
IVCT septal (ms)	54.76±7.42 55(40.67-73.94)	53.25±7.48 54.3(36.97-67)	55.83±9.83 55(40-86)	54.72±9.65 55.45(31.47-90.57)	0.564*
IVRT septal (ms)	55.45±9.95 55.23(35.12-85)	56.13±7.40 58(35-69)	55.37±8.59 55(39-79)	52.94±6.45 53.6(35.12-68.39)	0.265*
E/E' septal	7.11±1.36 7.05(4.37-10.55)	7.48±1.78 7.35(4.39-14.5)	7.07±1.43 7.15(4.05-11.5)	6.73±1.28 6.65(4.12-9.64)	0.104
S' lateral (cm/s)	10.79±2.32 10.8(6-17)	10.69±2.32 10.35(7-17.3)	10.76±3.39 10.1(6.17-28)	10.67±2.16 10.15(7-15)	0.857
E' lateral (cm/s)	19.86±4.09 19.5(10.5-27)	19.57±2.87 20(11.6-25.4)	18.57±3.35 18.55(12.5-26.2)	20.42±2.99 20(15-27.9)	0.065*
A' lateral (cm/s)	7.10±1.30 7(4.58-10)	7.58±2.10 7.21(5-17)	6.88±1.73 6.47(4.35-12.5)	6.75±1.73 6.55(4-14)	0.080
IVCT lateral (ms)	54.56±12.54 51.38(36.97-110.91)	52.13±7.92 52(36-70.24)	56.26±9.46 56(40-85)	54.98±9.76 52.41(36.97-77.63)	0.264
IVRT lateral (ms)	54.69±11.39 53.8(29.57-83)	54.47±8.81 53.8(33-70)	56.65±8.82 55.5(40-77)	51.13±8.50 51.73(33.27-68.39)	0.053
E/E' lateral	5.25±1.07 5.19(3.18-7.53)	5.18±1.05 4.95(3.64-8.27)	5.34±0.99 5.15(3.52-8.2)	5.07±1.07 5(3.02-8.1)	0.575

*Kruskal Wallis test, *One Way ANOVA test*A: Late diastolic flow velocity, A': Peak late diastolic wave velocity, E: Mitral early diastolic flow velocity, E': Peak early diastolic wave velocity, EDT: E wave deceleration time, EF: Ejection fraction, FS: Fractional shortening, IVCT: Isovolumetric contraction time, IVSd: Interventricular septal diastolic diameter, IVRT: Isovolumetric relaxation time, LA: Left atrium, LPWDd: Left posterior wall diastolic diameter, LVEDd: Left ventricular end diastolic diameter, S': Mitral annular peak systolic velocity, SD: Standart deviation, ATX: Atomoxetıne, MPH: Methylphenidate, ER: extended-release, OROS: osmotic-release oral system, Bold values denote statistical significance at the $p < 0.05$ level

Heart failure is classified in terms of systolic and diastolic dysfunctions of the heart. Systolic dysfunction is the condition when heart cannot pump blood to the body. The chambers of the heart enlarges with decrease in wall thickness. Diastolic dysfunction is the condition when there is not enough filling blood in the heart to pump accompanied with increase in pulmonary venous pressure. This finding can be explained with the impairment of left ventricular relaxation, increase in myocardial wall diameter and left ventricular stiffness.

The most commonly used measurements with echocardiography are the velocities of E and A waves. Patients with a normal left ventricle, had most of the diastolic filling in the early phase, which is expressed by the prominent E wave. Late phase represents atrial contraction and it is expressed by A wave. Since atrial contraction plays a lesser role in diastolic filling, the A wave is smaller than the E wave. However, if higher pressures are required for passive filling of the left ventricle, diastolic filling becomes more dependent on atrial contraction. Therefore, the velocity of A wave becomes higher than E wave. Evaluation of filling velocities is performed by measurement of E wave and A wave velocities, IVRT and calculation of E/A ratio.[30] IVRT is described as the time interval beginning with the closing of the aortic valve and ending with the opening of the mitral valve.[31]

Table 3. Post hoc analysis of the parameters with significance

	OROS-MPH vs. Controls	**OROS-MPH** vs. **ER-MPH**	**OROS-MPH** vs. **ATX**	**ER-MPH** vs. **Controls**	**ATX** vs. **Controls**	**ER-MPH** vs. **ATX**
A (cm/s)	0.291	0.013	**<0.001**	0.146	**0.007**	0.412
E/A	0.432	**0.001**	**<0.001**	0.023	**<0.001**	0.193
E' septal (cm/s)	0.044	0.174	0.317	**<0.001**	**0.002**	0.574
HR (min)	0.304	0.475	0.021	0.096	**0.002**	0.154
SBP (mmHg)	0.063	0.060	0.057	**0.001**	**0.001**	0.978
Duration of medication (month)	-	**<0.001**	**<0.001**	-	-	0.021
Dose of medication (mg/kg) **	-	**<0.001**	0.061	-	-	**<0.001**

*Mann-Whitney U test,**Tukey test, p<0,008 Bonferroni* A: Late diastolic flow velocity, E': Peak early diastolic wave velocity, HR: Heart rate, SBP: Systolic blood pressure, ATX: Atomoxetine, MPH: Methylphenidate, ER: extended-release, OROS: osmotic-release oral system, Bold values denote statistical significance at the p < 0.008 level

Filling patterns vary depending on the degree of the disease. In grade 1 diastolic dysfunction, there are relaxation changes characterized by smaller E waves, larger A waves, and increased E wave deceleration time. In grade 2 diastolic dysfunction, there is a pseudo-normalization pattern characterized by apparently normal E and A waves. In grade 3 or restrictive filling pattern, there is a very prominent E wave with a short and sharp deceleration time and a small A wave. The patients with grade 3 diastolic pattern have a significantly worse prognosis than others.[30] Furthermore, tissue Doppler imaging can be used to measure myocardial motion, specifically the amount the mitral annulus recoils towards the base during early diastole (E') and the wave associated with the phase of atrial contraction (A') reflecting myocardial relaxation.[32] The left ventricular filling pressures can be estimated by the E/E' ratio. The clinical findings associated with diastolic dysfunction of the left ventricle are dyspnea with exertion, ortopnea, tachypnea, tachycardia, pulmonary edema and are related with respiratory system. In the presence of diastolic dysfunction, left ventricular compliance decreases and over time, firstly the left ventricular pressure, then the left atrial pressure increases, and eventually left atrial dilatation develops. In diastolic dysfunction, blood is no longer pulled in by the left ventricle but instead is pushed by increased left atrial pressure.[32]

There are patients with heart failure as a result of coronary vasospasm during the use of MPH.[11] Systolic cardiac functions are evaluated with of ejection fraction, fractional shortening, IVCT, and S' parameters. IVCT is described as the time interval beginning with the closing of the mitral valve and ending with the opening of the aortic valve.[31] S' is defined as the wave when the cusps of the valve migrate towards the apex.[32] Parameters involving systolic functions were similar between the groups in the present study, indicating that conventional and Doppler parameters of systolic functions were preserved.

Ventricular diastolic functions are detected by means of Doppler and tissue Doppler parameters. Accordingly, a decrease in E and an increase in A with decreased E/A may be expected in the presence of diastolic dysfunction. Prolongation of IVRT and EDT also support the idea of diastolic dysfunction. E' is correlated with left ventricular relaxation, preload, and filling pressures. In normal hearts, left atrial pressure exerts a powerful effect on E' velocity. In addition to decrease in E', increase in E/E' is expected with diastolic dysfunction.[16,17,33] Tissue Doppler parameters are used for a more exact identification of diastolic dysfunction, since transmitral parameters alone do not correlate well with left ventricular filling pressures in patients with normal systolic function.[16] E/E' exhibits good correlation with left ventricular filling pressures in patients with cardiac disease. An apparent relationship between E' and relaxation of the left ventricle has been observed in both human and animal studies.[17] In case of impairment in left ventricular relaxation, E' is minimally affected by left ventricular filling pressures and preload. However, when relaxation of left ventricle is normal, E' is affected by preload. Therefore, in the patients with normal hearts, E' is affected by preload, while E/E' does not always correlate with left ventricular filling pressures. Structural changes in the left ventricle and left atrium may help to differentiate normal and abnormal diastolic functions.[17] MPH showed a dose-dependant increase in

D2 expression in myocytes,[25] which causes vaso-constriction and increase in left ventricular filling pressures.[29] The reference values of systolic and diastolic parameters evaluated in the study show a wide normality range in the literature related with the ages or body surface areas of the participants. Therefore the normality of these parameters should be evaluated whether according to age distribution or the mean values of age and gender matched controls like in our study. The OROS-MPH group had similar diastolic findings with controls. A study performed in Turkey, stated that children using OROS-MPH exhibited lower E' septal values than the controls, with no differences in other parameters indicating diastolic dysfunction.[14] The ATX group had higher A, lower E/A, lower E' septal than controls with similar E/E' septal and lateral, IVRT and EDT in our study indicating detoriation in more than one parameter representing diastolic function suggesting impairment in myocardial relaxation. The ER-MPH group had lower E' septal values than controls without any differences in the other diastolic parameters like the study previously performed in our country.

The ER-MPH group had lower E/A than the OROS-MPH group and similar findings with the ATX group. The ATX group had higher A and lower E/A than OROS-MPH group, suggesting that ATX medication may affect diastolic functions more than OROS-MPH. There was not a medication among these drugs that had an effect on all of the diastolic parameters but impairment of the other parameters may emerge overtime during clinical follow-ups.

According to the recommendations of the American Academy of Pediatrics, patients who receive ADHD medications should be monitored periodically in terms of HR and BP.[28] In view of the safety concerns described, it is also recommended to evaluate the patients before psychostimulant or non-stimulant therapy is initiated, together with personal histories of syncope, dizziness, palpitations and chest pain and family histories of premature sudden death, and with careful cardiac examination.[34] They should be referred for specialist cardiac evaluation if initial findings suggest such medical history or presence of cardiovascular disease. Patients should be monitored before and during treatment with BP and HR after every dose adjustment and at least every six months to detect clinically important increases. Tachycardia and hypertension caused by medication should be evaluated with a specialist cardiac evaluation to consider the need for beta-blockers and antihypertensive treatment. Atomoxetine and MPH should not be used in children suffering from severe cardiovascular or cerebrovascular disorders. They should not be used in the patients who have the risk for clinical deterioration, accompanied with increase in HR and SBP.[1]

Conclusions

To the best of our knowledge, this is the first study to evaluate the effects of OROS-MPH, ER-MPH, and ATX on systolic and diastolic functions together with a control group, in a pediatric population with ADHD. In our study, ATX use showed impairment in some of the diastolic findings supporting myocardial relaxation more than long acting-MPH medications. There was no apparent clinical findings in the children receiving the medications, also without changes in the rest diastolic parameters. When the results were subjected to clinical evaluation, we concluded that these findings were not sufficient enough to cause apparent cardiac dysfunction but these patients should be monitored to determine the changes in other diastolic parameters during time. Further studies should be performed to support the findings detected in our study.

Compliance with Ethical Standards

The methodology and questionnaire for this study were approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision number 2019-14-01). The authors assert that all procedures contributing to this work comply with the ethical standards of Bakırköy Dr. Sadi Konuk Training and Research Hospital and the Declaration of Helsinki of 1975, as revised in 2008.

Limitations

Heart rate is affected by numerous variables, such as noise and anxiety. It would therefore have been preferable to monitor HR using 24-hour Holter ECG, although it would not be practical to evaluate all the patients in this way.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

AMM, TK: Study idea, hypothesis, study design; AMM, TK: Material preparation, data collection and analysis; AMM: Writing the first draft of the article; AMM, TK: Critical review of the article finalization and publication process.

Financial Disclosure

None

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